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PRINCIPAL INVESTIGATOR: Max Harry Weil, M.D., Ph.D.

CONTRACTING ORGANIZATION: The Institute of Critical Care Medicine
Palm Springs, California 92262

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Max Harry Weil, M.D., Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The Institute of Critical Care Medicine
Palm Springs, California 92262

E-Mail: weilm@911research.org

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The goal of our task for the first year was to investigate whether the changes in sublingual PC02 reflect changes in tissue blood flow during hemorrhage and hemorrhagic shock. Hemorrhagic shock was induced by a modification of Wigger's method in male domestic pigs weighting 35 to 40 kg. Sublingual PCO_2 increased from 60 to 129 mmHg in parallel with average decreases in cardiac output to 44% and mean arterial pressure to 47% decreases in $EtCO_2$ from 35 to 28 mmHg together with increases in arterial blood lactate concentrations from 0.7 to 7.8 mmol/l over the two-hour interval of shock. Utilizing colored microspheres for measurements, siblingual blood flow decreased to 34% liver flow to 56% and renal flow to 47%. After reinfusion of shed blood, sublingual PCO_2 was restored to approximately baseline values together with arterial pressure, cardiac output and $EtCO_2$, but there was delayed reversal of lactic acidosis. In control animals, no significant changes were observed over the same time interval. Increases in sublingual PCO_2, is accompanied by proportionate decreases in sublingual and vital organ blood flows. Our study supports the rationale for non-invasive measurements of sublingual PCO_2 for diagnosis and quantitation of the severity of hemorrhagic shock.

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INTRODUCTION

Increases in tissue P_{CO_2} are associated with decreases in oxygen availability and utilization by vital cells (Johnson & Weil, 1991). Hydrogen ions are anaerobically generated as byproducts of lactic acid and from hydrolysis of adenosine triphosphate and adenosine biphosphate (Johnson & Weil, 1991). When the hydrogen ions are buffered by intracellular HCO_3^-, CO_2 is generated. The high diffusability of CO_2 facilitates surface measurements of tissue P_{CO_2} (Gutierrez, 1992). The early clinical focus was on the gastric wall utilizing gastric tonometry. The rationale was based on the assumption that the viscera and especially the stomach, liver, and intestines were the earliest organs that reflected critical decreases in blood flow during hemorrhagic shock states (Dantzker, 1991; Chendrasekhar, 1996; Kivilaakso, 1982; Maynard, 1993; Reilly 1992).

In settings of critical low-flow states of circulatory shock, the carbon dioxide tensions (P_{CO_2}) of the stomach wall, the liver parenchyma, the kidneys, the myocardium and the cerebral cortex were increased early. Tissue hypercarbia was promptly reversed after restoration of normal blood flow (Desai, 1993, 1995; Johnson, 1995; Kette, 1993; Tang,). Studies also by our group subsequently demonstrated that esophageal wall P_{CO_2} and sublingual P_{CO_2} measurements yielded values comparable to those of gastric P_{CO_2} for estimation of the severity of circulatory shock (Sato, 1997).

Since hypercarbia was equally profound in the intra-abdominal viscera and the extra-abdominal sites in settings of circulatory shock (Sato, 1997), we were alerted to the likelihood that tissue hypercarbia was a general phenomenon of perfusion failure. This challenged the established assumption that the intra-abdominal organs were early and selective target organs (Fiddian-Green, 1987). Sublingual P_{CO_2} became a practical noninvasive option for monitoring P_{CO_2} in lieu of gastric tonometry (Jin, 1998; Nakagawa, 1998; Weil, 1999; Povoas, 2001). We then demonstrated comparable reductions in blood flow to the gastric wall and to the jejunum, colon, kidneys, and to the tongue and sublingual mucosa in rats during hemorrhagic shock. These findings provided evidence that tissue hypercarbia was a general rather then a primary visceral phenomenon of perfusion failure and explained proportionately comparable reductions in tissue blood flow at intra-abdominal and extra-abdominal sites of measurement (Jin, 1998).

This study represents the work to date of our award DAMD17-02-1-06. Our goal was to confirm our hypotheses that changes in sublingual PCO2 reflect changes in vital organ blood flow during low flow states of hemorrhage and hemorrhagic shock.

STUDY PERFORMED

The study was approved by the Animal Care and Use Committee of the Institute of Critical Care Medicine. All animals received humane care in compliance with the Animal Welfare Act Regulations and other Federal statutes relating to animals and experiments involving animals and adheres to the principles set forth in the Guide for Care and Use of Laboratory Animals, National Research Council, 1996.

Animal preparation. Ten healthy male Yorkshire-X domestic pigs (Sus scrofa) aged 5-6 months, weighing between 35 and 40 kg, were supplied by a single source breeder who has consistently supplied healthy animals of relatively uniform age and weight. All animals were fasted overnight except for free access to water. Anesthesia was initiated by intramuscular injection of 20 mg/kg of ketamine and completed by ear vein injection of 30 mg/kg sodium pentobarbital. Additional doses of 8

mg/kg sodium pentobarbital were administered by bolus intravenous injections at intervals of approximately one h or when required to maintain anesthesia. A cuffed endotracheal tube was advanced into the trachea with the aid of direct laryngoscopy. Animals were mechanically ventilated with a tidal volume of 15 ml/kg, a peak flow of 40 l/min and FiO_2 of 0.21 with a volume-controlled ventilator (Model MA-1, Puritan-Bennett, Carlsbad, CA). End-tidal PCO_2 ($EtCO_2$) was measured with an infrared main stream analyzer (Model O1R-7101A, Nihon Kohden Corp, Tokyo, Japan). Respiratory frequency was adjusted to maintain $EtCO_2$ between 35 and 40 mmHg. The conventional frontal plane electrocardiogram was continuously recorded.

For measurement of aortic pressure, a fluid-filled 8F angiographic catheter (Model 6523; USCI, C.R. Bart Inc., Billerica, MA) was inserted into the surgically exposed left femoral artery and advanced into the descending thoracic aorta. For the measurements of right atrial pressure and for measurements of cardiac output by the thermodilution method, together with measurement of core (blood) temperature, a 7F pentalumen, thermodilution-tipped catheter (Abbott Critical Care #41216, Salt Lake City, Utah) was advanced from the surgically exposed right femoral vein and flow-directed into the pulmonary artery. For injection of colored microspheres, a 5F angiographic catheter (Model AR2, Boston Scientific Scimed Inc., Maple Grove, MN) was advanced from the left carotid artery to the left ventricle. A 14F cannula (William Harvey model 1848 USCI; CR Bart Inc; Billerica, MA) was advanced into the abdominal aorta through the right femoral artery for bleeding. Another 14F cannula was inserted into the right femoral vein for the reinfusion of shed blood. The position of the catheters was confirmed by both characteristic pressure-pulse morphology and with the aid of fluoroscopy. All catheters were flushed periodically with physiologic salt solution containing 10 IU/ml of bovine heparin. The right femoral artery cannula was connected to a 2-liter sterile reservoir for bleeding and reinfusion, and continuously measured in the pulmonary artery. Blood temperature was maintained at 37 ± 0.5 C utilizing infrared surface heating lamps.

For the measurement of $PslCO_2$ we utilized an optical CO_2 sensor (Capnoprobe, Model 2000, OSI, Minneapolis, MN). The sensor was calibrated in a water-filled tonometer maintained at 34.5 C ± 0.5 C. For calibration, gas mixtures of 5% and 20% CO_2 in nitrogen allowed for two- point calibration. The sensor was applied under direct vision to the mucosa of the right sublingual space of the pig.

Experimental procedure. Baseline measurements were obtained prior to randomization to the hemorrhage or sham-hemorrhage control group by the sealed envelope method. Hemorrhagic shock was induced by a modification of the Wigger's method. Blood was aseptically collected through preheparinized catheters and delivered to a sterile 2-liter reservoir containing 4,000 IU heparin. The blood was shed at a rate of approximately 20 ml/min and manually agitated over an interval of over 60 min until the mean arterial pressure was reduced to 55 ± 5 mmHg. The pressure in the reservoir was adjusted to maintain arterial pressure at 55 mm Hg for an additional 60 min. After 2 h, the blood was reinfused at a rate of 100 ml/min with the aid of an infusion pump over an average interval of 14 min. At 2 h after reinfusion of the shed blood, animals were euthanized with an intravenous injection of 150 mg/kg of pentobarbital. Autopsy was routinely performed to confirm catheter positions, to exclude injuries to the thoracic and abdominal organs, and to exclude coincident disease. For control animals, the procedure was identical except that no blood was allowed to flow from the femoral artery catheter into the reservoir.

Organ blood flow was measured with an adaptation of the colored-microsphere technique as previously reported (Hale, 1988; Jin, 1998). An estimated 5×10^6 microspheres, with a mean diameter of 15 ± 2 μm, colored with red, green, blue, and orange (E-Z TRAC, Los Angeles, CA) were suspended in 5 ml

of normal saline and agitated with a vortex mixer (37600 mixer, Thermolyne, Dubuque, IA). The suspensions were manually injected into the left ventricle over an interval of 15 sec. Beginning 30 sec prior to the injection of microspheres, blood was withdrawn with the aid of a peristaltic pump of our own design at a rate of 6 ml/min. Measurements were obtained prior to hemorrhage (baseline) and, at 60 and 120 min during hemorrhagic shock and at 120 min after reinfusion of shed blood. At autopsy, tissue was sampled in amounts estimated to yield statistically appropriate concentrations of microspheres, namely samples of 3 to 13 grams of tissue from the sublingual site of P_{CO_2} measurement, the buccal mucosa, the diaphragmatic surface of the right lobe of the liver, the anterior wall of the left ventricle and the mid cortex of both kidneys. The tissue was weighed and then digested overnight with the E-Z TRAC digestive reagent I, at a temperature of 60^0C. The suspension was then delivered to 15 ml centrifuge tubes and centrifuged at 3,000 rpm for 30 min (Marathon 21K, Fischer Scientific, Pittsburgh, PA). The sediment containing the microspheres was resuspended in the E-Z TRAC digestive reagent II and recentrifuged for 15 min. The sediment was again suspended but this time in the E-Z TRAC counting reagent. The suspension was then transferred to a glass tube of known weight and again centrifuged for 15 min. The sediment was then suspended in the counting reagent and reconstituted to a volume of between 150 and 350 µl. The weight of the tube was then measured with an optical balance (Magnigrad, Type 21, Ainsworth & Sins, Denver, CO). Aliquots of this suspension were delivered to an improved Neubauer hemocytometer chamber for counting. The same procedures were utilized on the blood which had been withdrawn from the aorta prior to and during injection of the microspheres.

Measurements. Dynamic data, including aortic, right atrial, pulmonary artery and pulmonary occlusive pressures, $EtCO_2$, and lead II of the electrocardiogram were continuously measured and recorded on PC-based data acquisition system, supported by CODAS hardware/software (DATAQ Instruments, Akron, OH) as previously described (28). A total of 16 channels were provided for continuous recording at appropriate sampling frequencies for the proposed study. Cardiac output was measured by the conventional thermodilution method after injection of 5 ml of physiological salt solution at a temperature of $< 3^0$C, utilizing a cardiac output computer (Model 3300; Abbott Critical Care Systems). Measurements were obtained at baseline and at intervals of 30 min after start of hemorrhage. Aortic and mixed venous blood gases, hemoglobin and oxyhemoglobin together with blood lactate, were measured on samples of 400 µl of blood utilizing a blood gas analyzer (Model Stat Profile Ultra C, Nova Biomedical Corporation, Waltham, MA). Arterial blood lactate was measured on 200 µl aliquot with a lactic analyzer (Model 23L, Yellow Springs Instruments, Yellow Springs, OH). These measurements were obtained at baseline and at hourly intervals for a total of 4 h.
Organ blood flow was computed, as follows:

$$Q_o\ (ml \cdot min^{-1}) = \frac{C_{To} \cdot Q_{bw}}{C_{Tb}}$$

In which Q_o represents organ blood flow, C_{To} total numbers of microspheres in the organ sample, Q_{bw} amount of withdrawn blood from the abdominal aorta ($ml \cdot min^{-1}$) , and C_{Tb} is the total number of microspheres in the blood withdrawn. Organ blood flow (Q_{ow}) per 100 g of tissue was calculated as follows:

$$Q_{ow}\ (ml \cdot min^{-1}) = \frac{Q_o \cdot 100}{\text{sample weight (g)}}$$

Statistical analyses. For measurements between groups, ANOVA and Scheffe's multicomparison techniques were used. Comparisons between time-based measurements within each group were performed with ANOVA repeated measurements. Measurements were reported as means ± SD. A value of $p < 0.05$ was considered significant.

KEY ACCOMPLISH AND OUTCOMES

There were no differences in baseline hemodynamic, blood gas, blood lactate, or end-tidal P_{CO_2} measurements between the control sham hemorrhage and hemorrhagic shock groups, nor in the computed blood flow to tissues in the sham hemorrhage control group over the interval of study (Table1 and Fig. 1). $P_{sl}CO_2$ in the hemorrhagic shock group increased from 61 to 129 mmHg during hemorrhage, buccal P_{CO_2} increased from 56 to 116 mmHg, mean arterial pressure (MAP) decreased from an average of 115 to 57 mmHg, and cardiac output (CO) from 6.1 to 2.8 $L \cdot min^{-1}$. Reinfusion of shed blood restored MAP and, excepting a transient overshoot, the cardiac output, to near-baseline levels. Arterial blood lactate concentrations increased from 0.7 to 7.8 mmol/l, but failed to return to baseline values at the end of 4 h (Fig. 2).

Following hemorrhage, the sublingual tissue blood flow decreased to 31%, the buccal mucosa blood flow to 29%, the liver blood flow to 47% and the kidney blood flows to between 43 to 49% of baseline values (Table 1 and Fig. 1). This contrasted with myocardial flow during hemorrhagic shock which was reduced to only 71% of baseline values. Increases in $P_{sl}CO_2$ were highly correlated with decreases in sublingual blood flow ($r = 0.78$), buccal mucosa blood flow ($r = 0.82$), liver blood flow ($r = 0.66$) and renal blood flow ($r = 0.72$) (Fig. 3). As anticipated, no significant differences between right and left kidneys were observed. Significantly greater blood flow was maintained in the heart in comparison to more profound reductions in the sublingual and buccal sites ($p<0.01$) and to the kidneys ($p<0.05$) (Table 2). At two h after reinfusion of shed blood, both tissue $P_{sl}CO_2$ and organ blood flows had returned to approximately baseline, preshock values (Fig. 1).

CONCLUSION

We conclude that increases in sublingual P_{CO_2} are explained by proportional decreases in blood flows not only in the viscera but at more accessible sites in the mouth. The rationale for technically simple and non-invasive measurements indicative of the onset and severity of hemorrhagic shock utilizing the oral mucosa is therefore further secured. The present studies provide further evidence that changes in sublingual P_{CO_2} during hemorrhagic shock reflects change in vital organ blood flow.

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FIGURE LEGENDS

Figure 1: Comparisons of values of blood flow in various tissues, together with time coincident increases and decreases in sublingual and buccal mucosal P_{CO_2}. BL= baseline, ** $P<0.01$ vs. baseline.

Figure 2: Changes in the measured values of cardiac output, mean arterial pressure, end-tidal CO_2, and arterial blood lactate prior to, during, and after reversal of hemorrhagic shock. BL= baseline; * $P<0.05$, ** $P<0.01$ vs. control.

Figure 3: Relationships among the measured values of sublingual P_{CO_2} and concurrent measurement of blood flows to the kidneys, the liver, and the buccal and sublingual mucosa. The right kidney is represented by open circles and the left kidney by closed circles.

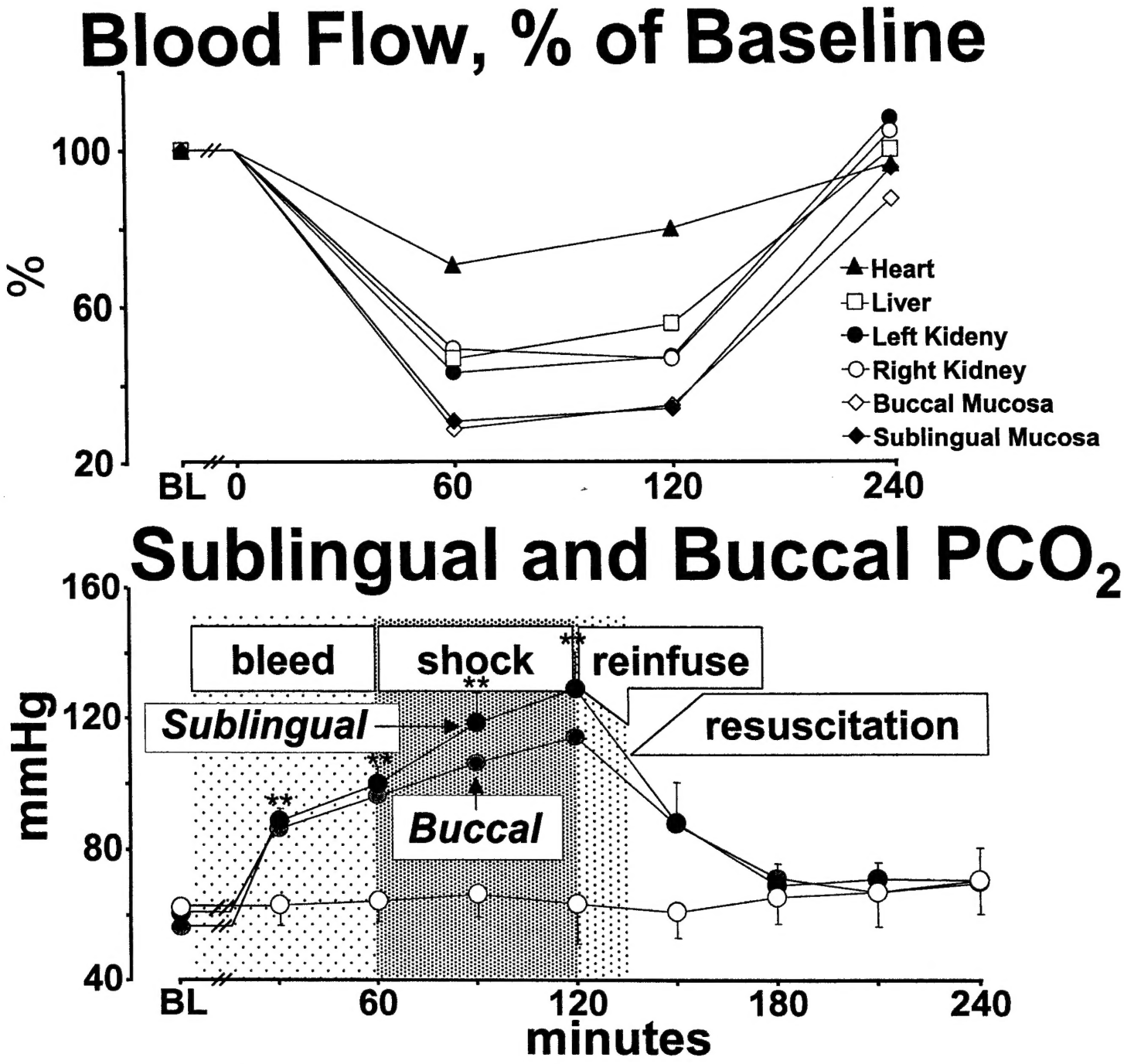
Blood Flow, % of Baseline
100
60
20
%
BL
0
60
120
240
Heart
Liver
Left Kideny
Right Kidney
Buccal Mucosa
Sublingual Mucosa
Sublingual and Buccal PCO2
160
120
80
40
mmHg
bleed
shock
reinfuse
resuscitation
Sublingual
Buccal
**
BL
60
120
180
240
minutes

FIGURE 1

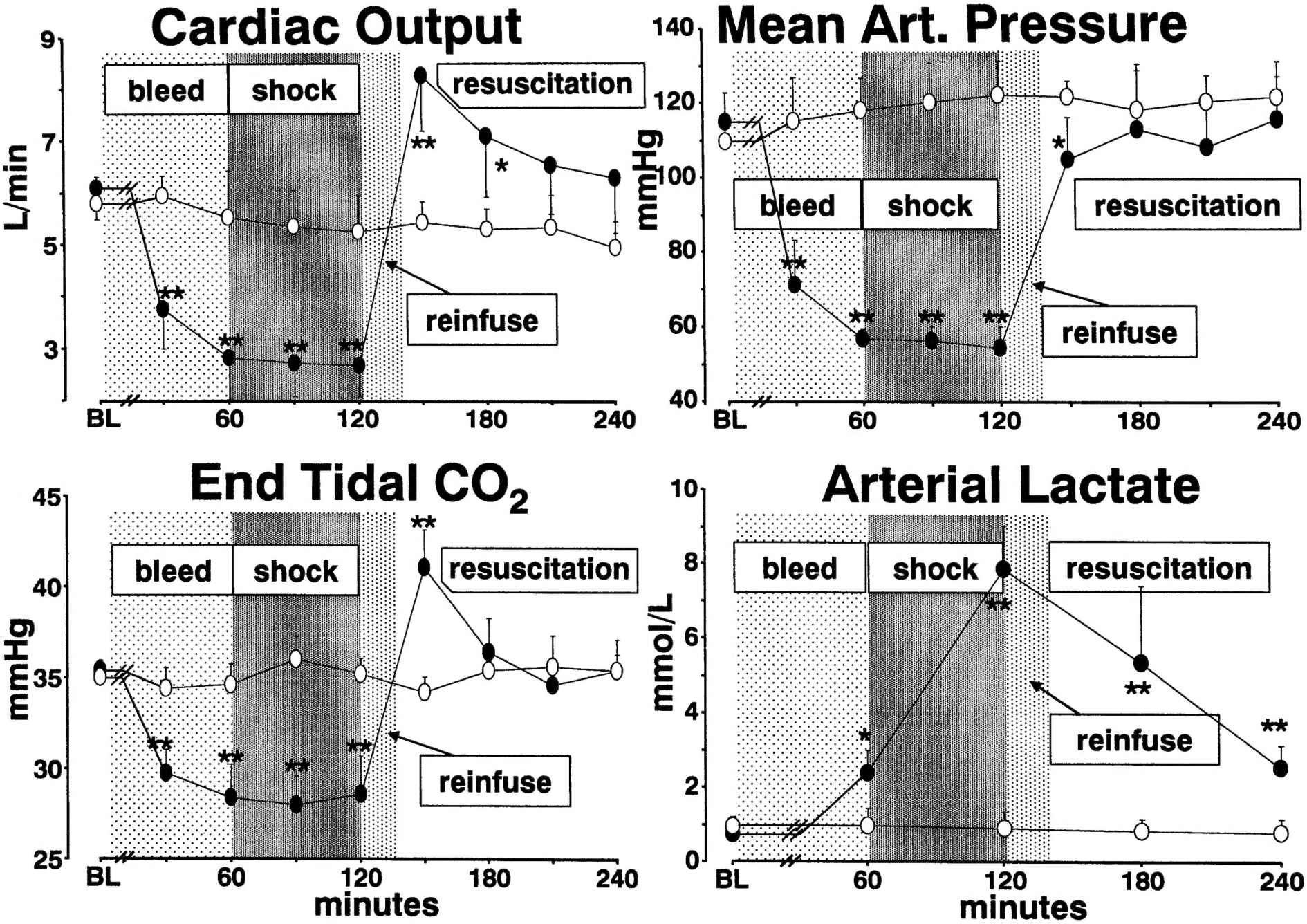
Cardiac Output
L/min
9
7
5
3
bleed
shock
resuscitation
reinfuse
BL
60
120
180
240
Mean Art. Pressure
mmHg
140
120
100
80
60
40
bleed
shock
resuscitation
reinfuse
BL
60
120
180
240
End Tidal CO_2
mmHg
45
40
35
30
25
bleed
shock
resuscitation
reinfuse
BL
60
120
180
240
minutes
Arterial Lactate
mmol/L
10
8
6
4
2
0
bleed
shock
resuscitation
reinfuse
BL
60
120
180
240
minutes

FIGURE 2

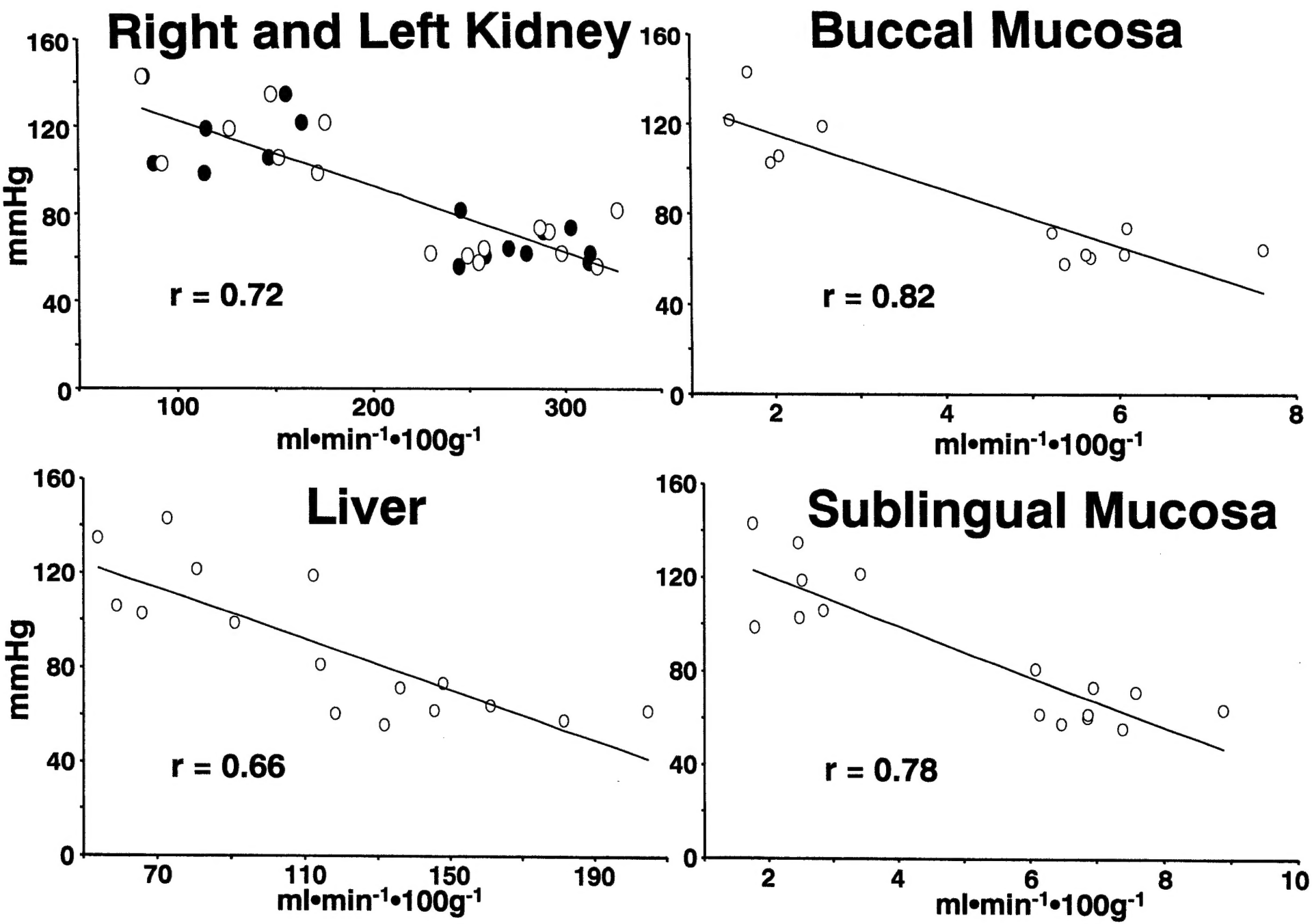
Right and Left Kidney
mmHg
160
120
80
40
0
r = 0.72
100
200
300
ml•min-1•100g-1
Buccal Mucosa
r = 0.82
2
4
6
8
Liver
r = 0.66
70
110
150
190
Sublingual Mucosa
r = 0.78
10

FIGURE 3

Table 1: Tissue Blood Flows

Tissue	Group	Baseline ml/min/100g	60 min ml/min/100g	60 min %Baseline	120 min ml/min/100g	120 min %Baseline	240 min ml/min/100g	240 min %Baseline
Sublingual	Hemorrhage	7.2 ± 1	2.2 ± 0.5†	31 ± 6	2.5 ± 0.6†	34 ± 7	6.9 ± 0.6	95 ± 7
	Sham	7.8 ± 1.3	7.1 ± 1.0	91 ± 11	6.9 ± 1.0	89 ± 12	7.0 ± 0.8	91 ± 10
Buccal	Hemorrhage	6.3 ± 0.9	1.8 ± 0.4†	29 ± 5	2.2 ± 0.7†	35 ± 10	5.5 ± 0.4	87 ± 6
	Sham	5.6 ± 0.5	5.7 ± 0.5	102 ± 8	5.3 ± 0.6	94 ± 10	5.8 ± 0.3	102 ± 5
Liver	Hemorrhage	152 ± 33	71 ± 14†	47 ± 7	85 ± 24†	56 ± 13	152 ± 29	100 ± 15
	Sham	154 ± 21	148 ± 24	96 ± 14	158 ± 24	103 ± 14	148 ± 12	96 ± 7
Heart	Hemorrhage	180 ± 16	128 ± 24*	71 ± 12	144 ± 13*	80 ± 6	173 ± 30	96 ± 15
	Sham	167 ± 25	171 ± 22	103 ± 11	174 ± 24	104 ± 12	164 ± 29	98 ± 15
Left Kidney	Hemorrhage	274 ± 26	118 ± 24†	43 ± 8	130 ± 32†	48 ± 11	294 ± 30	108 ± 10
	Sham	274 ± 26	265 ± 29	99 ± 10	286 ± 34	108 ± 13	265 ± 18	100 ± 6
Right Kidney	Hemorrhage	271 ± 36	134 ± 35†	49 ± 12	127 ± 37†	47 ± 12	282 ± 32	104 ± 10
	Sham	284 ± 20	259 ± 21	91 ± 7	285 ± 35	101 ± 12	272 ± 41	96 ± 13

Values are means ± SD, significant difference from control in same tissue, * $P < 0.05$; † $P < 0.01$.

Table 2: Tissue Blood Flows, % of Baseline. Comparison between tissues.

Tissue	Group	60 min	120 min	240 min
Heart	Hemorrhage	71 ± 12	80 ± 6	96 ± 15
Sublingual	Hemorrhage	31 ± 6†	34 ± 7†	95 ± 7
Buccal	Hemorrhage	29 ± 5†	35 ± 10†	87 ± 6
Left Kidney	Hemorrhage	43 ± 8*	48 ± 11†	108 ± 10
Right Kidney	Hemorrhage	49 ± 12*	47 ± 12 *	104 ± 10

Values are means ± SD, significant difference from heart tissue, * P <0.05; † P < 0.01.